thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound is capable of inhibiting the interaction.--

--18. (Amended) The method of claim 1, wherein the compound is a [polyepetide] polypeptide, a nucleic acid, or an inorganic chemical.--

REMARKS

Claims 1-57 were pending in the subject application. Applicants have hereinabove amended claim 1. Support for the amendment to claim 1 may be found, *inter alia*, at page 7, lines 9-24 in the specification. Applicants have hereinabove amended claim 18 to correct an obvious typographical error. Support for the amendment to claim 18 may be found, *inter alia*, at page 14, line 22 in the specification. Applicants have amended the specification to correct a obvious typographical error. Applicants maintain that the above-mentioned amendments to the claims and specification raise no issue of new matter.

Election/Restriction

The Examiner acknowledged applicants' election with traverse of Group I, claims 1-13 and 15-29 in Paper No. 6. The Examiner stated that the traversal is on the ground(s) that it would not be a burden for the Examiner to search Groups I-IV together since such groups do not define distinct inventions, and a search of

the prior art for the subject matter defined by the claims in any one of Groups I-IV would necessarily overlap and possibly identify art pertaining to the subject matter defined by claims in any of the other Groups. The Examiner stated that this is not found persuasive because:

under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05 - § 806.05(I); and

(B) There must be a serious burden on the Examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(I), § 808.01(a), and § 808.02).

The Examiner stated that the term "distinct" means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use or sale as claimed, **and are patentable** (novel and unobvious) **over each other** (though they may each be unpatentable because of the prior art). The Examiner stated that it will be noted that in this definition the term related is used as an alternative for dependent in referring to subjects other than independent subjects. (MPEP § 802.01). The Examiner stated that where inventions are related as disclosed but are distinct as claimed, restriction may be proper (MPEP § 806(B)). The Examiner stated that in the instant case the four inventions are related but distinct.

The Examiner stated that consistent with current patent practice, a serious search burden may be established by (A) separate

classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. The Examiner stated that the four inventions, though related, would require non-coextensive literature searches. The Examiner stated that further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. The Examiner stated that thus, the four groups require divergent searches, and to search all four inventions would be burdensome. The Examiner stated that, therefore, the restriction is maintained.

The Examiner stated that the requirement is still deemed proper and is therefore made FINAL.

Species Election

The Examiner acknowledged applicants' election of the following species in Paper No. 8, filed April 13, 2000: (a) peptide: carboxymethyl-lysine modified; (b) derivatization of the peptide: alkyl; and (c) compound: polypeptide.

The Examiner withdrew claims 3, 9, 10, 14, 16, 19, 23 and 30-57 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The Examiner stated that applicant timely traversed the restriction (election)requirement in Paper No. 6.

The Examiner stated that claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29 will be prosecuted on the merits. Thus, upon entry of the present amendment, claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29 will be pending and under examination in the subject application.

Specification

The Examiner stated that the disclosure is objected to because of the following informalities:

The Examiner stated that the word polypeptide on page 9, line 10 is misspelled.

The Examiner stated that on page 13, line 3, the last word "pepetide" is misspelled.

The Examiner stated that appropriate correction is required.

In response, applicants have amended the specification to correct the obvious typographical errors pointed out by the Examiner. Applicants believe that the amendments to the specification obviate the Examiner's objection and respectfully request that the objection be withdrawn.

Claim Rejections - 35 USC §112

Rejection under 35 U.S.C. 112, first paragraph

The Examiner rejected claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) using the full length receptor or the V-domain of the receptor, does not reasonably provide enablement for any other receptor fragment. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the

invention commensurate in scope with these claims.

The Examiner stated that the claims encompass a competitive binding assay using RAGE, or a fragment of RAGE. The Examiner stated that on page 8, lines 11-21 of the instant specification, a fragment of RAGE is defined as being at least 5 amino acids in length. The Examiner stated that the specification teaches that the V-domain of RAGE, comprising amino acids 1-120 of the full length protein (which is 404 amino acids in length), and soluble RAGE, comprising the extracellular two-thirds of the amino acid sequence of membrane-bound RAGE, can bind to various advanced glycation end products such as CML-BSA and be used in a competitive binding assay. The Examiner stated, however, that given that a fragment of RAGE can be as small as 5 amino acids in length, and that the disclosure does not provide examples of experiments using RAGE fragments smaller that the V-domain or sRAGE, one of skill in the art would not expect a fragment as small as 5 amino acids to be capable of binding an advanced glycation end product and so be useful in the assay.

The Examiner stated that this rejection could be overcome by insertion of a functional limitation in claim 1, such as, for example in section (a) (ii): "RAGE or a fragment of RAGE that can bind the peptide".

In response, without conceding the correctness of the Examiner's position, but to expedite prosecution of the subject application, applicants have amended claim 1 in accordance with the Examiner's suggestion. Applicants maintain that the amendment to claim 1 obviates the Examiner's rejection of claim 1 under 35 U.S.C. 112, first paragraph. Accordingly, applicants respectfully request

that the Examiner reconsider and withdraw the rejection.

Rejection under 35 U.S.C. 112, second paragraph

The Examiner rejected claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that claim 18 is indefinite because "polyepetide" is not a word.

In response, applicants have hereinabove amended claim 18 to correct the obvious typographical error pointed out by the Examiner. Applicants believe that the amendment to claim 18 obviates the Examiner's rejection under 35 U.S.C. 112, second paragraph. Therefore, applicants respectfully request that Examiner reconsider and withdraw this rejection.

Claim Rejections - 35 USC § 102

Rejection under 102(e)

The Examiner rejected claims 1, 2, 5-8, 13, 15, 17, 18, 20-22 and 24-28 under 35 U.S.C. 102(e) as being anticipated by Morser et al., U.S. Patent No. 5,864,018, filing date April 16, 1996.

The Examiner stated that claims 1, 2, 5-8, 13, 15, 17, 18, 20-22 and 24-28 encompass a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay, comprising admixing the peptide (wherein the amino groups are inactivated by chemical derivatization) with RAGE or a fragment of RAGE in the presence and the absence of the compound, wherein the peptide is an AGE or fragment thereof that is carboxymethyl-lysine, modified, synthetic, the peptide is

derivatized via chemical modification resulting in an alkyl derivative or is synthetic, and wherein the RAGE or RAGE fragment is synthetic, soluble or comprises the V-domain, wherein the compound is sRAGE, a polypeptide, a polyclonal or monoclonal, humanized, chimeric or privatized antibody, and wherein the peptide or RAGE is affixed to a solid surface, and the peptide or RAGE is labeled.

The Examiner stated that Morser et al. teaches a method of using the AGE/RAGE interaction in order to screen test compounds in order to identify agonists or antagonists of the AGE/RAGE interaction. The Examiner stated that in column 16, line 29 to column 17, line 54, Morser et al. teaches that test compounds may be chemical compounds, biological macromolecules, or extracts made from biological materials such as bacteria, plants, fungi, or animal cells or tissues, and test compounds will typically include the polypeptides or fragments of the present invention (AGEs and RAGE or sRAGE or RAGE fragment) as well as structural analogs or peptidomimetics which are derived from these polypeptides or the antibodies described in the patent, and substrates or ligands thereof (column 16, lines 15-44).

The Examiner stated that in column 16, line 50 to column 17, line 15, Morser et al. teaches that the screening methods typically involve incubation of RAGE with an advanced glycosylation end-product protein (AGE, a derivatized, inactivated protein) such as AGE-BSA, nonenzymatically N-glycosylated collagen, myelin or the like, as well as the test compound, and that typically, one of the RAGE polypeptide or AGE will be immobilized upon a solid support which will then be contacted with the other protein or peptide, and that the one of the pair will include a labeling

group such as radiolabels, chemiluminescent or flourescent groups (column 9, lines 44-54).

The Examiner stated that in column 5, lines 24-28, Morser et al. teaches that soluble RAGE polypeptides generally comprise fragments of the extracellular domain of RAGE, and the soluble peptides will comprise one or more of the IG-like domains of the extracellular region of RAGE (the V-domain). The Examiner stated that in column 6, lines 41-52, Morser et al. also teaches that the polypeptides may also be characterized by their ability to block the interaction between two proteins, and include peptides derived from RAGE such as fragments which encompass AGE binding regions of RAGE as well as AGE-binding proteins.

The Examiner stated that in column 5, lines 33-38, Morser et al. teaches that the polypeptides may be characterized by their ability to either mimic or inhibit the interaction between AGEs and their receptors (RAGE), and that those polypeptides which are mimetic of either AGE or its receptors in the AGE/receptor interaction are termed AGE or AGE receptor "mimics".

The Examiner stated that Morser et al. in column 10, line 6 to column 11, line 56 teaches antibodies that bind with relative high affinity to RAGE, and can be used for a number of purposes, including inhibiting interaction between AGEs and their receptors, and that these antibodies can be monoclonal, polyclonal, fragments, chimeric or humanized. The Examiner stated that in column 7, lines 22-35, Morser et al. teaches that the polypeptides of the invention may be prepared using synthetic methods.

The Examiner stated that therefore, from teachings of Morser et al., claims 1, 2, 5-8, 11-13, 15, 17, 18, 20-22 and 24-28 are anticipated.

In response, applicants respectfully traverse Examiner's rejection of claims 1, 2, 5-8, 11-13, 15, 17, 18, 20-22 and 24-28 under 35 U.S.C. 102(e). Applicants' assert that Morser, et al. does not disclose every limitation of applicants' claimed invention. Applicants' claimed invention is directed to, *inter alia*, a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises: (a) admixing: (i) the peptide, wherein amino groups of the peptide are inactivated by chemical derivitization, (ii) RAGE or a fragment thereof which is capable of binding the peptide, and (iii) the compound; (b) determining the amount of the peptide bound to RAGE or the fragment thereof, and (c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound is capable of inhibiting the interaction. Morser, et al. does not describe the steps of admixing a peptide, <u>wherein amino groups of the peptide are inactivated by chemical derivitization</u> with a compound and a RAGE or fragment thereof, nor does it therefore disclose a method of determining the amount of such a peptide bound to the RAGE, followed by a qualitative comparison of bound and unbound peptide used to determine the compound's ability to inhibit the

interaction between the peptide and RAGE. Applicants point out that "inactivated by derivitization" is described in the applicants' specification at page 12, lines 21-24, as encompassing a chemical modification of a peptide so as to cause amino groups of the peptide to be less reactive with the chemical modification than without such chemical modification. Morser, et al. does not disclose peptides so modified and therefore does not disclose applicants' claimed method.

Applicants respectfully maintain, therefore, that Morser, et al., does not anticipate applicants' claimed invention. Accordingly, applicants respectfully request that Examiner reconsider and withdraw the rejection of claims 1, 2, 5-8, 11-13, 15, 17, 18, 20-22 and 24-28 under 35 U.S.C. 102(e).

Rejection under under U.S.C. 102(b)

The Examiner rejected claim 29 under U.S.C. 102(b) as being clearly anticipated by Stern et al., WO 97/26913, July 31, 1997.

The Examiner stated that claim 29 encompasses a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) in a competitive assay, comprising admixing the peptide (wherein the amino groups are inactivated by chemical derivatization) with RAGE or a fragment of RAGE in the presence and the absence of the compound, and wherein the assay occurs in a cell.

The Examiner stated that Stern et al. teach a method for evaluating the ability of an agent to inhibit binding of an amyloid-β peptide (derivatized, inactivated peptide) with a

receptor for advanced glycation end product on the surface of a cell which includes contacting the cell with the agent and amyloid-β peptide, determining the amount of amyloid-β peptide bound to the cell and comparing the amount of bound amyloid-β peptide with the amount determined in the absence of the agent (see abstract, page 3, page 13 and claims 49-51. Therefore, the Examiner stated that Stern et al. clearly anticipates claim 29.

In response, applicants respectfully traverse Examiner's rejection of claim 29 under 35 U.S.C. 102(b). Applicants' claimed invention is directed to, *inter alia*, a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises: (a) admixing: (i) the peptide, wherein amino groups of the peptide are inactivated by chemical derivitization, (ii) RAGE or a fragment thereof which is capable of binding the peptide, and (iii) the compound; (b) determining the amount of the peptide bound to RAGE or the fragment thereof, and (c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound is capable of inhibiting the interaction, wherein step (a) occurs in a cell. Applicants maintain that Stern, et al. does not anticipate claim 29 of applicant's invention. Specifically, Stern et al. does not disclose inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises: (a) admixing: (i) the peptide, <u>wherein</u>

amino groups of the peptide are inactivated by chemical derivitization, (ii) RAGE or a fragment thereof which is capable of binding the peptide, and (iii) the compound, nor does Stern et al disclose a RAGE not located on a cell surface. Applicants therefore maintain that applicants' claimed invention is not anticipated by Stern, et al. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 29 under 35 U.S.C. 102(b).

Claim Rejections - 35 USC § 103

The Examiner rejected claims 4, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Morser et al. and further in view of Reddy et al., Biochemistry, Vol. 34, pp 10872-10878, 1995 (cited in IDS).

The Examiner stated that the teachings of Morser et al. are described above. The Examiner stated that Morser et al. differs from claims 4, 11 and 12 in that they do not specifically teach carboxymethyl-lysine-modified peptides in the assay method.

The Examiner stated that Reddy et al. teaches that carboxymethyl-lysine is a dominant advanced glycation end product (AGE) antigen in proteins.

The Examiner stated that given that carboxymethyl-lysine modified peptides are a dominant AGE, it would have been *prima facie* obvious to one of skill in the art of AGE/RAGE art at the time of the invention to use carboxymethyl-lysine-modified peptide of Reddy as the AGE in the AGE/RAGE competition assay of Morser et al. to determine whether a compound is capable of inhibiting the AGE/RAGE interaction. The Examiner stated that Morser et al.

teaches that since AGES have been implicated in a variety of disorders including complications associated with diabetes and normal aging, and because of the effects AGEs may have in the pathogenesis of a number of disorders, it would generally be desirable to provide compositions and methods to block or otherwise inhibit these effects, and particularly the interaction between AGEs and their cell surface receptors (columns 1-2).

In response, applicants respectfully traverse Examiner's rejection of claims 4, 11, and 12 under 35 U.S.C. 103(a). Applicants' claimed invention is directed to, *inter alia*, a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE), which comprises: (a) admixing: (i) the peptide, wherein amino groups of the peptide are inactivated by chemical derivitization, (ii) RAGE or a fragment thereof which is capable of binding the peptide, and (iii) the compound; (b) determining the amount of the peptide bound to RAGE or the fragment thereof, and (c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or fragment thereof, wherein a reduction in the amount of binding in the presence of the compound indicates that the compound is capable of inhibiting the interaction, wherein the peptide is a carboxymethyl-lysine-modified AGE, the peptide derivative of step (a)(i) comprises an alkyl derivative, or wherein the alkyl derivative comprises an acetyl derivative, a propyl derivative, an isopropyl derivative, a butyl derivative, an isobutyl derivative, or a carboxymethyl

derivative. As discussed hereinabove, Morser, et al. describes a method which is not the method recited in the claims of applicants' invention. Morser, et al. teaches a method that differs from applicants' claimed invention in ways in addition to those acknowldeged by the Examiner.

Moreover, applicants emphasize to Examiner the great heterogeneity of AGEs and peptides which are capable of binding to RAGE or a fragment thereof. As the Examiner notes, Reddy, et al. discloses a particular AGE, (N^{ϵ}-(carboxymethyl)lysine out of the many known in the art. Moreover, some such peptides are pathogenic while others are not. There are, therefore, many potential combinations of peptides wherein amino groups of the peptide are inactivated by chemical derivatization and RAGE which exist and it is not obvious which, if any, of these combinations are pathogenic. Given the number and variety of such possible combinations, one of ordinary skill would not be motivated to choose any particular such combination and from there develop a method of determining whether a compound is capable of inhibiting the interaction, such as the method of applicants' claimed invention. Inhibiting one particular interaction between a particular peptide and RAGE does not enable one to accurately determine which potential compounds are capable of inhibiting the interaction of one or more of the many other potential peptide-RAGE combinations. One would therefore not be motivated based on the cited references to choose a particular peptide/RAGE interaction for which to determine which compounds might be capable of inhibiting that interaction. In that regard, applicants' claimed invention would clearly not have been obvious to one of ordinary skill in the art at the time of the invention.

Applicants maintain, therefore, that there is no motivation in the references to combine the Morser and Reddy references. Even if one were to follow the Examiner's logic in combining the references, (although applicants do not concede the correctness of this logic), one would not arrive at the claimed invention. Using the AGE described in Reddy in the method described in Morser, one would not arrive at the applicants' claimed invention because the method described in Morser does not include the limitations or steps recited in the claims of applicants' presently claimed invention as discussed hereinabove. Therefore, applicants maintain that the Morser and Reddy references, either alone or in combination do not render obvious applicants' claimed invention. Accordingly, applicants respectfully request that Examiner reconsider and withdraw the rejection of claims 4, 11, and 12 under 35 U.S.C. 103(a).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $445.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. If any other fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

1/5/01
John P. White Date
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